

Clinical Translation of Ultrasound-Guided Photoacoustic Imaging

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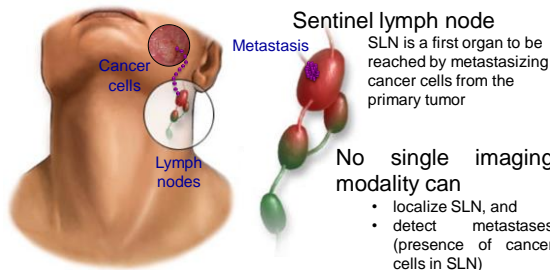


Department of Imaging Physics
The University of Texas M.D. Anderson Cancer Center

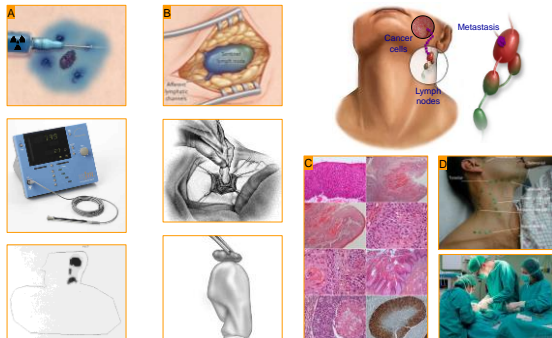


Detection of Micrometastases in Sentinel Lymph Node (SLN)

Primary tumor metastasizes through lymphatic system
Melanoma, Breast cancer, Head and neck squamous carcinoma

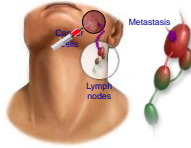


Detection/Characterization/Treatment of SLN using Imaging/Biopsy/Surgery



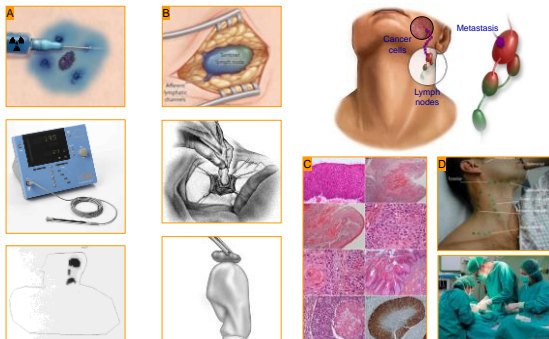
Detection/Characterization of SLN using Imaging/Biopsy

- Dye and radioactive tracer are injected near the tumor
- Contrast agent is allowed to drain to lymph nodes
- Lymphoscintigraphy is performed to identify the sentinel node
- **Biopsy** is performed to sample sentinel lymph node
- If positive for micrometastatic cancer cell, sentinel and axillary lymph nodes are surgically removed

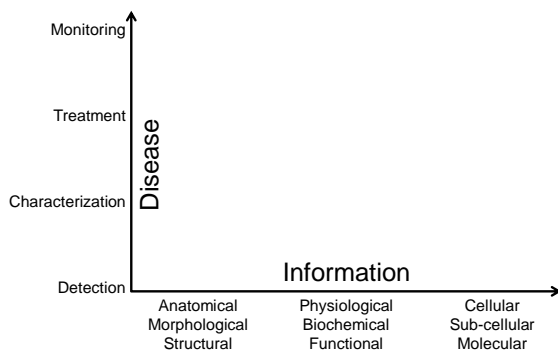


- Highly effective
- Accurate prognosis
- May take up to 2 weeks
- Invasive
- Requires multiple specialists (nuclear medicine, surgery, pathology)

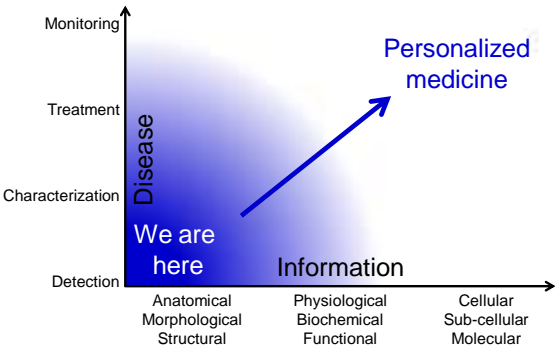
Detection/Characterization/Treatment of SLN using Imaging/Biopsy/Surgery



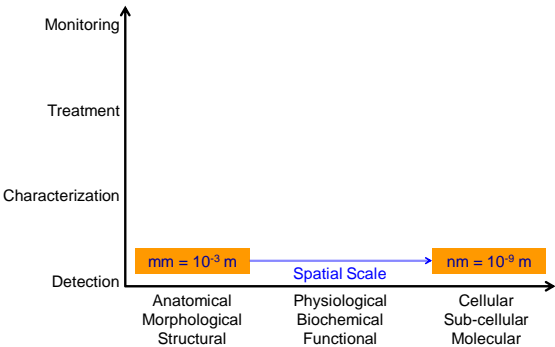
Disease Management



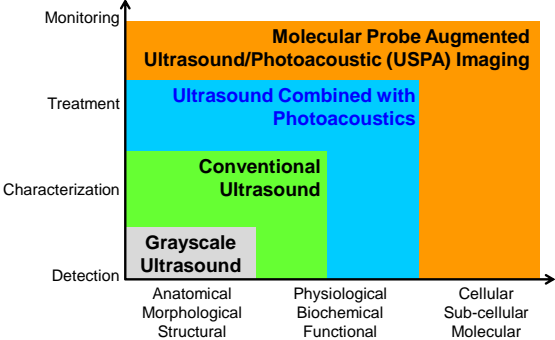
Disease Management: Problem



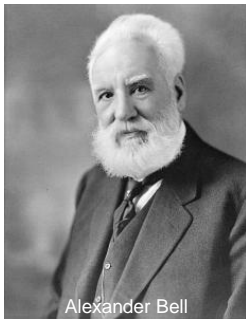
Disease Management: Challenge



Solution: Ultrasound and Photoacoustics



Photoacoustics Imaging and Sensing: Alexander Bell, 1980

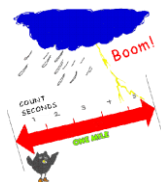
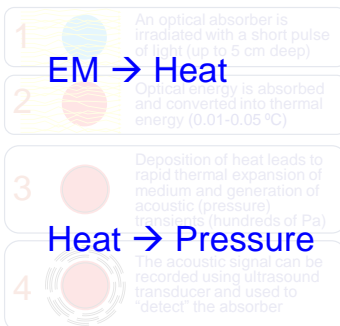


A. Bell and C. Tainter, 1880





Photoacoustics: Lightning and Thunder



Photoacoustics Imaging Lightning and Thunder



Photoacoustics Imaging Lightning and Thunder

- 1  An optical absorber is irradiated with a short pulse of light (up to 5 cm deep)
- 2  Optical energy is absorbed and converted into thermal energy (0.01-0.05 °C)
- 3  Deposition of heat leads to rapid thermal expansion of medium and generation of acoustic (pressure) transients (hundreds of Pa)
- 4  The acoustic signal can be recorded using ultrasound transducer and used to "detect" the absorber

$$F(z) = F_0 \cdot e^{-\mu_{\text{eff}} \cdot z}$$

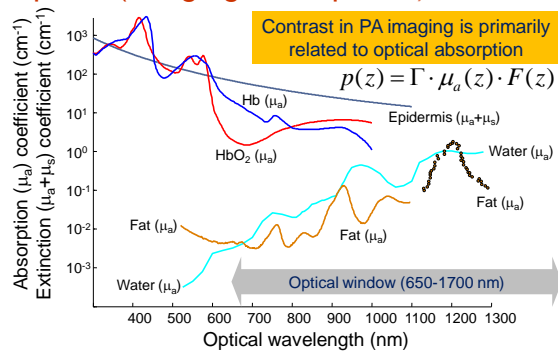
$$DT(z) = \frac{m_a(z)F(z)}{\Gamma \cdot C_p}$$

Incompressibility
small $DT \leftrightarrow$ large P

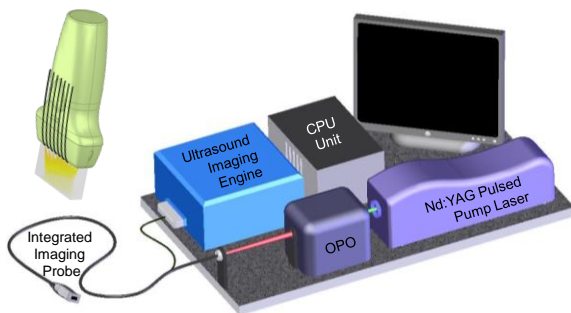
$$p(z) = \Gamma \cdot \mu_a(z) \cdot F(z)$$

$$z = V_{\text{sound}} \cdot t$$

Photoacoustic Imaging: Optical (Imaging/Therapeutic) Window



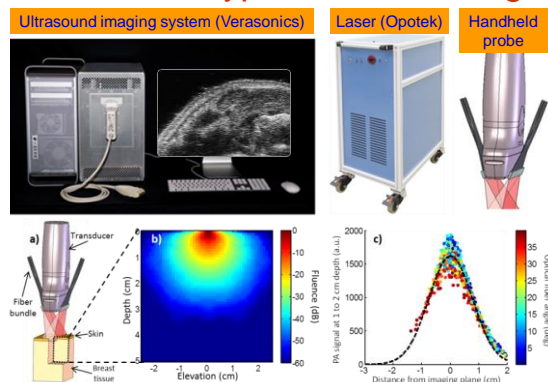
Integrated USPA Imaging System (Ultrasound and Photoacoustics)



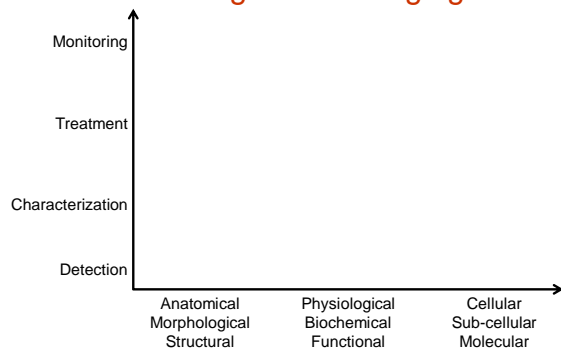
Integrated USPA Imaging System (Ultrasound and Photoacoustics)



Clinical Prototype of USPA Imager

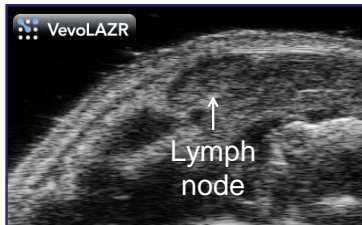


Detection/Characterization/Therapy of SLN using USPA Imaging

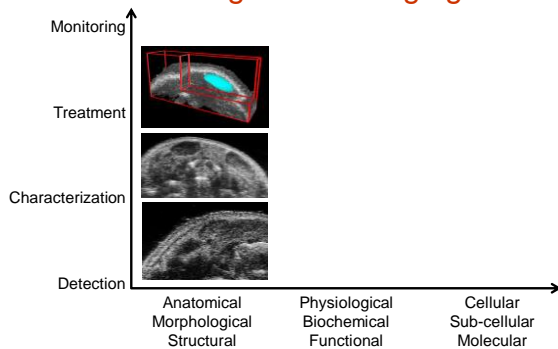


Mouse Model of Metastatic Oral Cancer

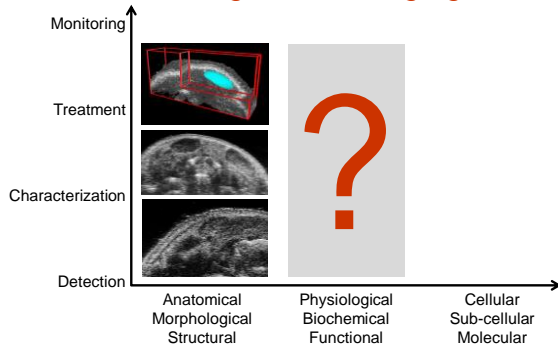
- Primary tumor in a tongue of a mouse
- After 2-3 weeks, micrometastatic foci are formed in sentinel lymph node(s)



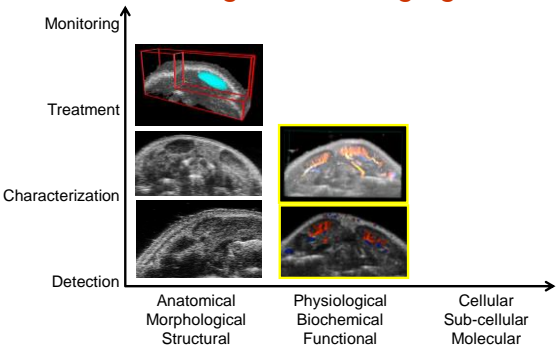
Detection/Characterization/Therapy of SLN using USPA Imaging



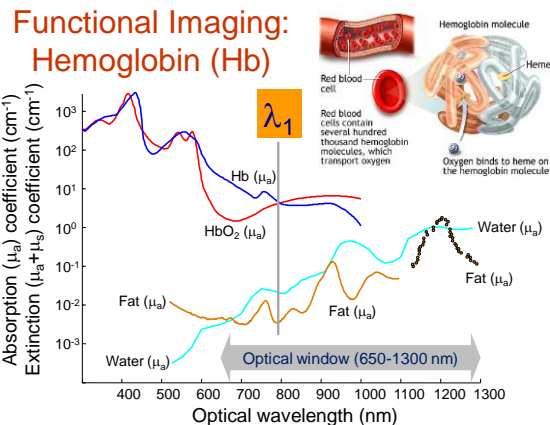
Detection/Characterization/Therapy of SLN using USPA Imaging



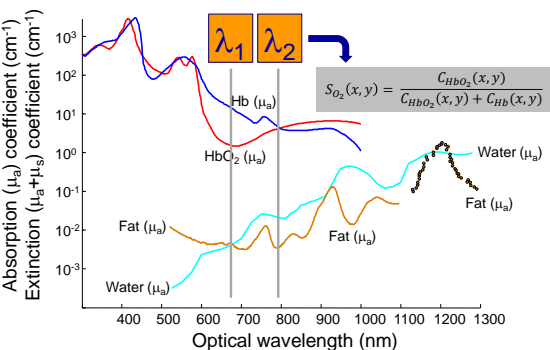
Detection/Characterization/Therapy of SLN using USPA Imaging



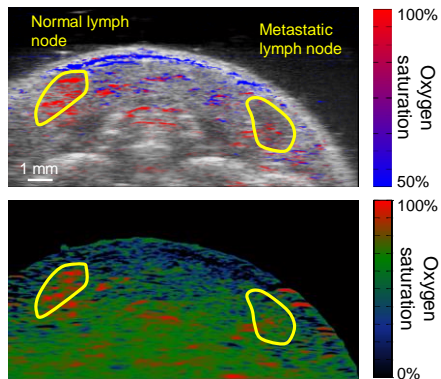
Functional Imaging: Hemoglobin (Hb)



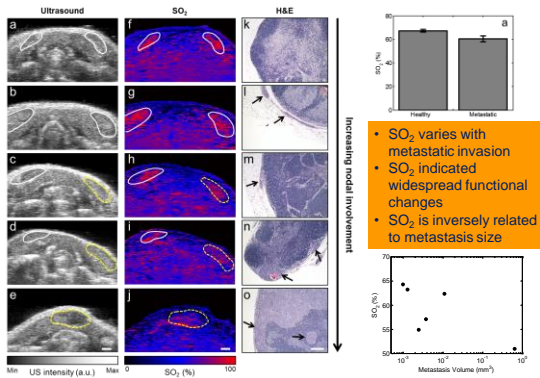
Functional Imaging: Total Hemoglobin and Oxygen Saturation



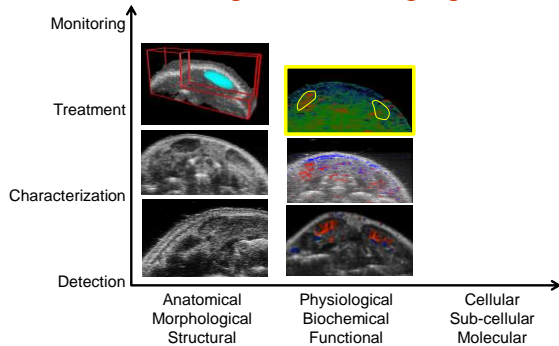
Detection/Characterization of SNL



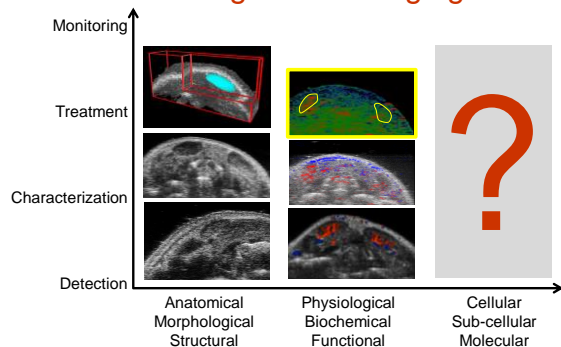
Detection/Characterization of SNL



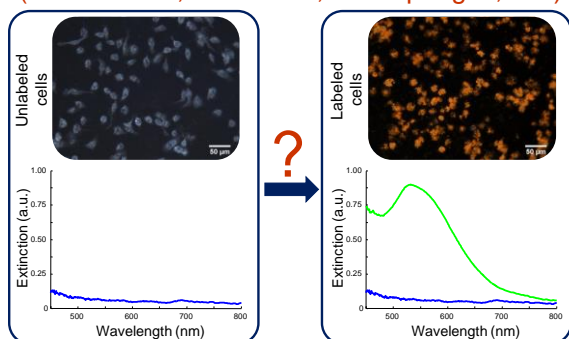
Detection/Characterization/Therapy of SLN using USPA Imaging



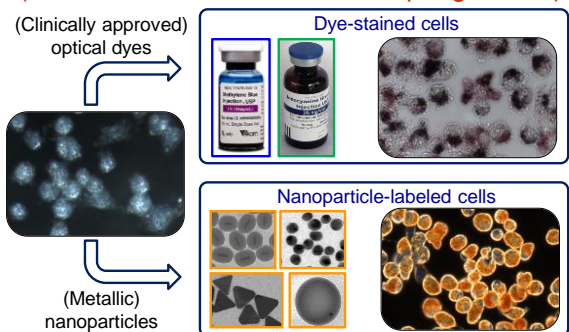
Detection/Characterization/Therapy of SLN using USPA Imaging



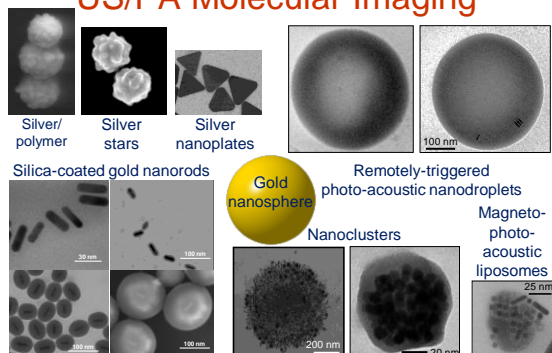
Cellular/Molecular Imaging (Cancer cells, Stem cells, Macrophages, etc.)



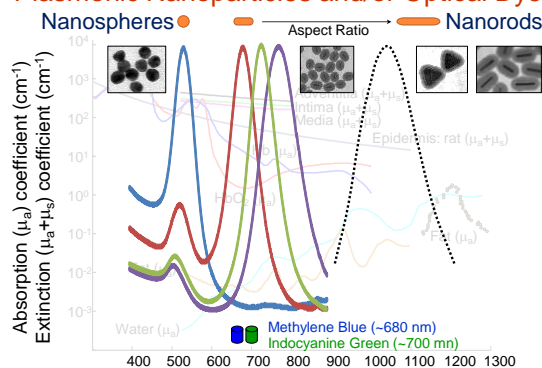
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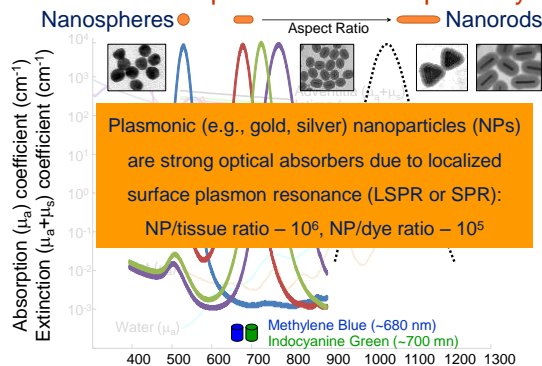
Contrast nanoAgents for US/PA Molecular Imaging



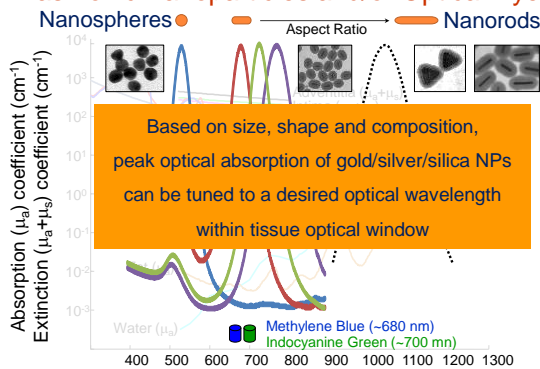
Contrast Agents for Molecular US/PA Imaging: Plasmonic Nanoparticles and/or Optical Dyes



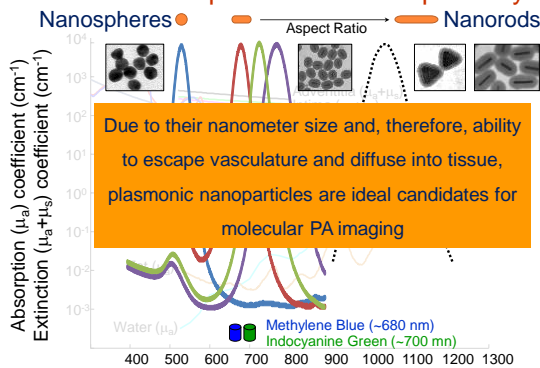
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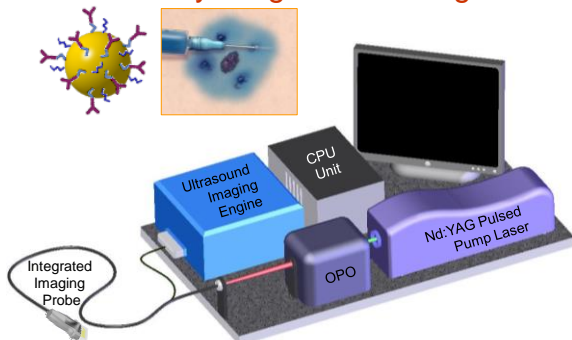
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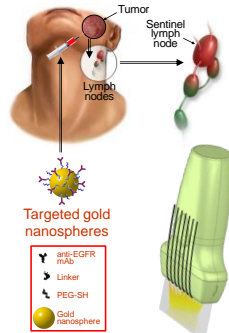


Ultrasound/Photoacoustic Imaging with Molecularly Targeted NanoAgents



Detection and Characterization of SLN using Molecular USPA Imaging

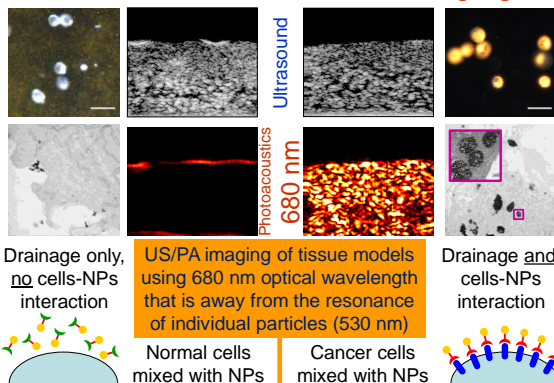
- Cocktail of optical dye and targeted gold nanospheres are injected near the tumor
- Contrast agent is allowed to drain to lymph nodes
- Ultrasound-guided photoacoustic (USPA) imaging is performed to identify
 - the sentinel node
 - cancer cells within the node



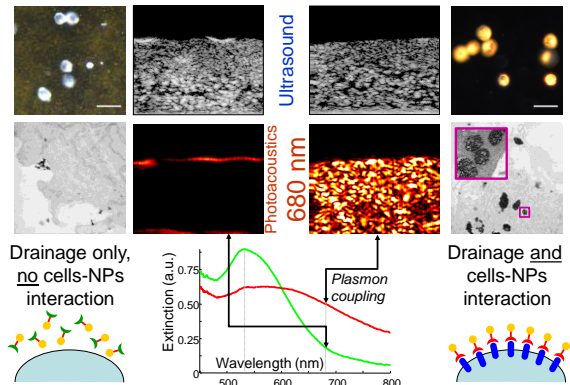
Detection of Micrometastases in Sentinel Lymph Node (SLN)

- We have developed an approach based on
 - Gold nanospheres targeted to phenotype of the primary tumor (peak absorption at ~530 nm)
 - Ultrasound-guided spectroscopic photoacoustics
- In this approach
 - Nanoparticles are injected near the tumor and allowed to drain to lymph node (SLN)
 - US/PA imaging is performed within 680-750 nm wavelength range to identify receptor-mediated endosytosed nanoparticles

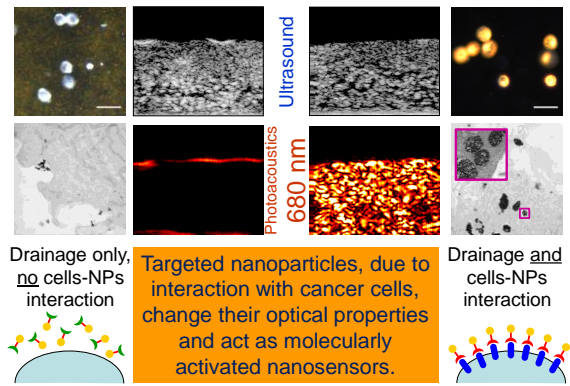
Molecular Photoacoustic Imaging



Molecular Photoacoustic Imaging

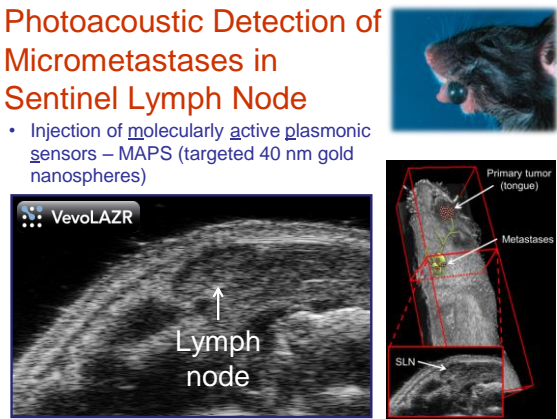


Molecular Photoacoustic Imaging

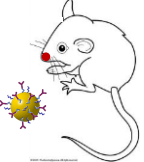
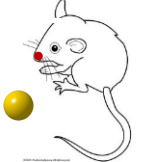
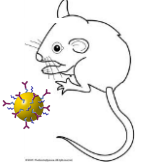


Photoacoustic Detection of Micrometastases in Sentinel Lymph Node

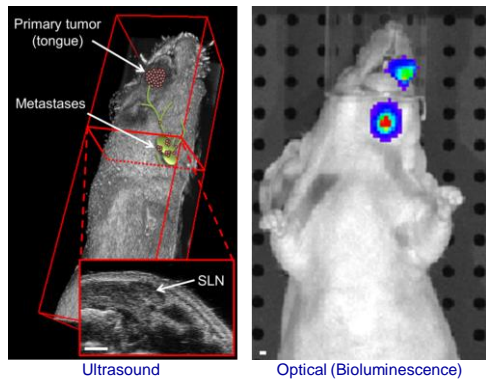
- Injection of molecularly active plasmonic sensors – MAPS (targeted 40 nm gold nanospheres)



In-Vivo Mouse Imaging Studies

Group A Match	Group B Mismatch	Group C No match
EGFR-positive tumor and mets	EGFR-positive tumor and mets	No tumor (normal mouse)
EGFR targeted nanospheres	RG16 targeted nanospheres	EGFR targeted nanospheres
		

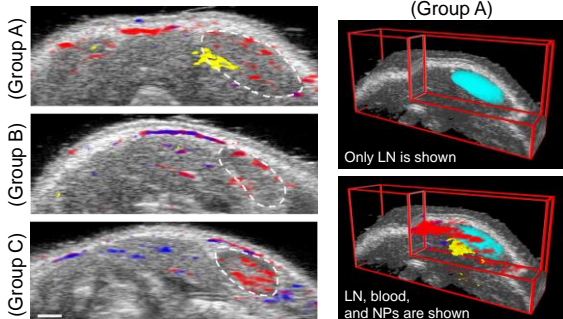
Metastatic Mouse Model



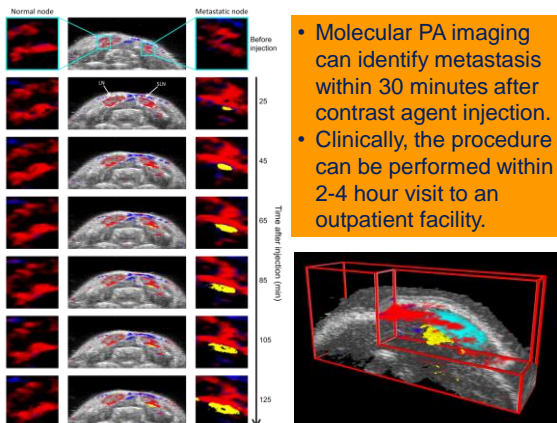
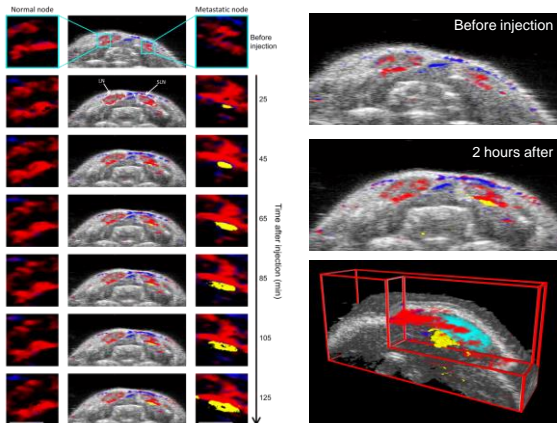
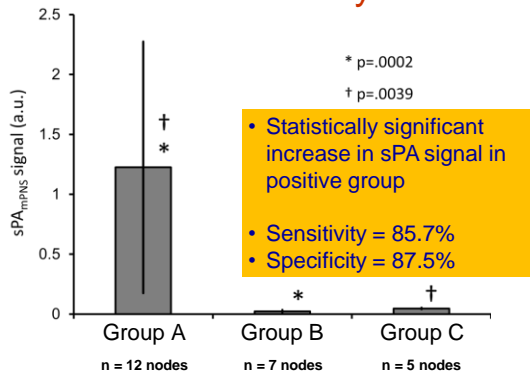
In-Vivo Mouse Imaging Studies

Representative comparison between three groups

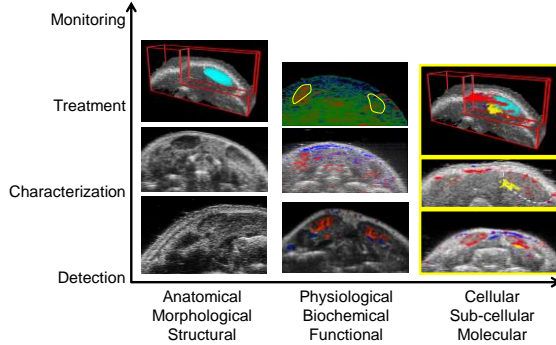
3-D USPA images, cut-away view (Group A)



Statistical Analysis

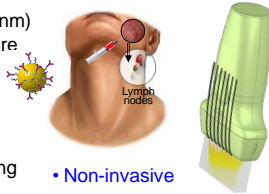


Detection/Characterization/Therapy of SLN using USPA Imaging



Detection/Characterization of SLN and Treatment of Axillary Lymph Nodes

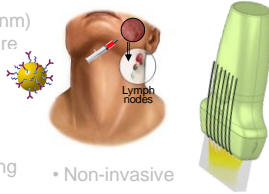
- ❖ Cocktail of dye and small (5-nm) targeted gold nanospheres are injected near the tumor
- Contrast agent is allowed to drain to lymph nodes
- ❖ Ultrasound-guided photoacoustic (USPA) imaging is performed to identify
 - the sentinel node
 - cancer cells within the node
- If positive for micrometastatic cancer cell, sentinel and axillary lymph nodes may be removed



- Non-invasive
- Non-ionizing
- Accurate
- Cancer specific
- Immediate

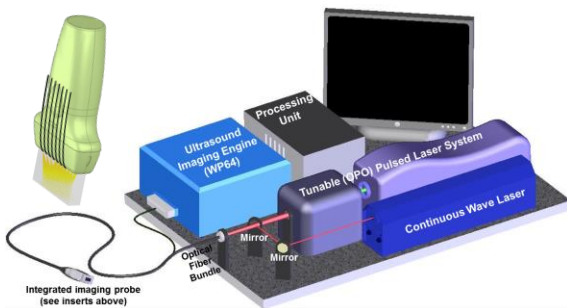
Detection/Characterization of SLN and Treatment of Axillary Lymph Nodes

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- Contrast agent is allowed to drain to lymph nodes
- Ultrasound-guided photoacoustic (USPA) imaging is performed to identify
 - the sentinel node
 - cancer cells within the node
- Photothermal therapy

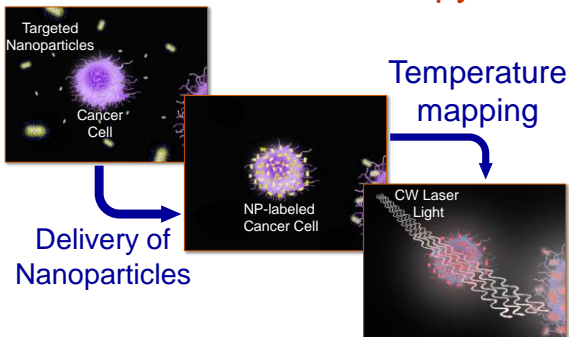


- Non-invasive
- Non-ionizing
- Accurate
- Cancer specific
- Immediate
- Imaging → Therapy

Integrated US/PA Imaging and Image-Guided Therapeutic System



Role of USPA Imaging in Photothermal Therapy



Thermal Imaging using Photoacoustics

- The photoacoustic signal is given by

$$p(z) = \Gamma \cdot \mu_a \cdot F(z)$$

- The Gruneisen parameter is temperature-dependent

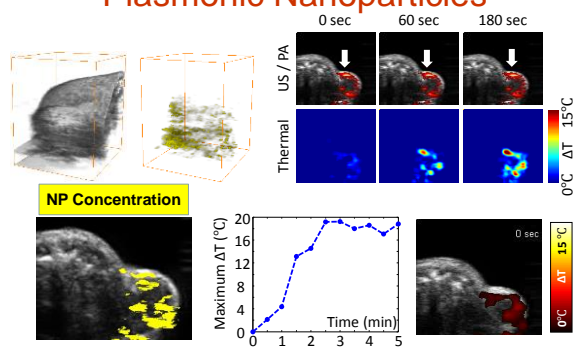
$$\Gamma(T) = \frac{\beta(T) \cdot c(T)^2}{C_p}$$

$\beta(T)$: thermal expansion coefficient
 $c(T)$: speed of sound
 C_p : heat capacity

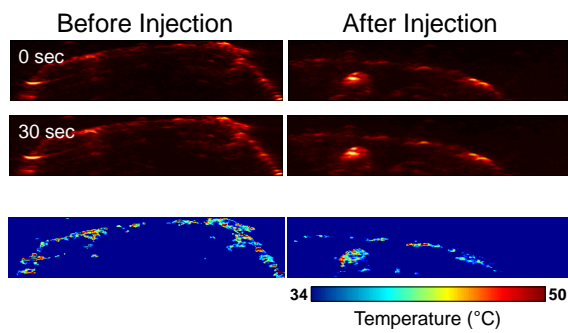
- Therefore, PA pressure $p(z, T) \leftrightarrow$ temperature T

$$p(z, T) = \Gamma(T) \cdot \mu_a \cdot F(z) = (a + bT) \cdot \mu_a \cdot F(z)$$

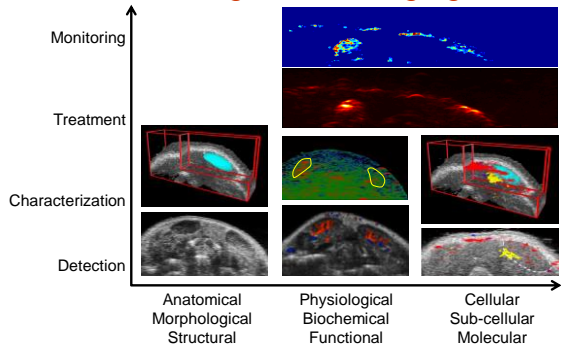
Photothermal Therapy using Plasmonic Nanoparticles



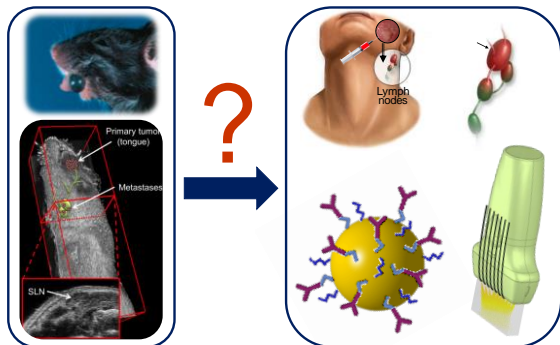
Photothermal Therapy using Plasmonic Nanoparticles



Detection/Characterization/Therapy of SLN using USPA Imaging



Detection/Characterization of SLN and Treatment of Micrometastases



Clearance of Nanoparticles

Diameter: 20 ~ 150 nm



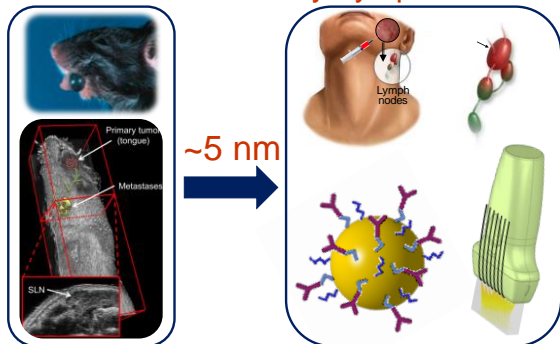
Diameter: less than 5.5 nm



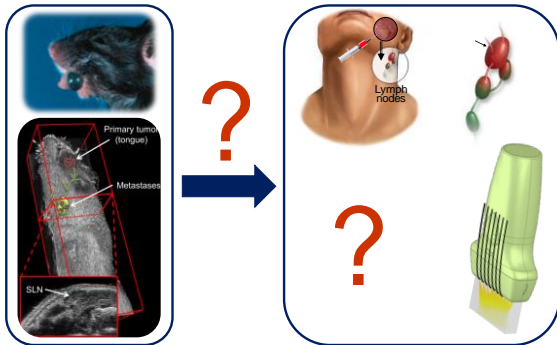
Particles smaller than 5.5 nm in diameter are rapidly cleared by kidney from the body!

Choi, H.S. et al. *Nature Biotechnology* (2007)

Detection/Characterization of SLN and Treatment of Axillary Lymph Nodes

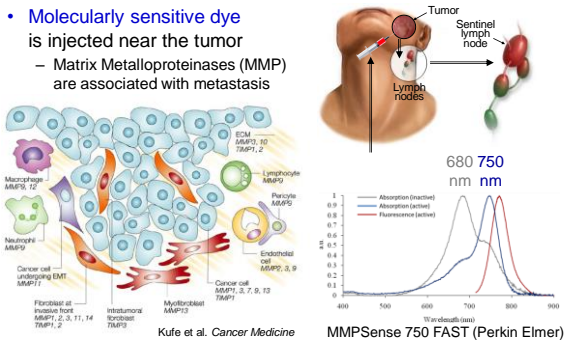


Detection/Characterization of SLN and Treatment of Micrometastases

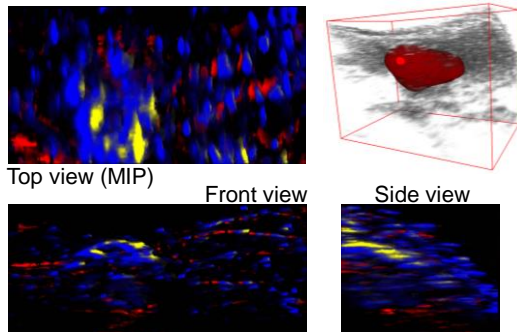


Detection and Characterization of SLN using Molecular USPA Imaging

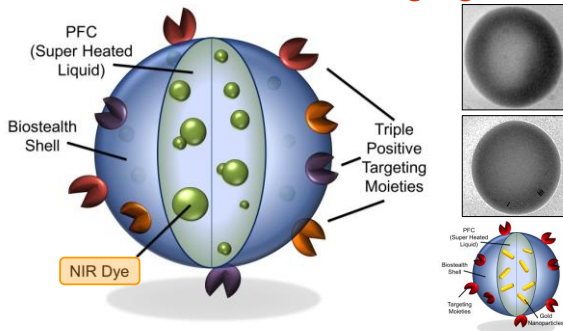
- Molecularly sensitive dye is injected near the tumor
 - Matrix Metalloproteinases (MMP) are associated with metastasis



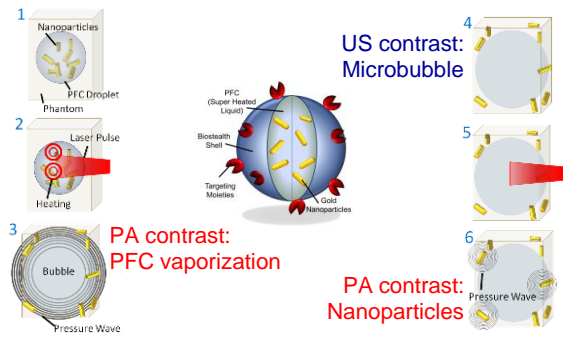
Drainage and Activation of MMP-sensitive Dye



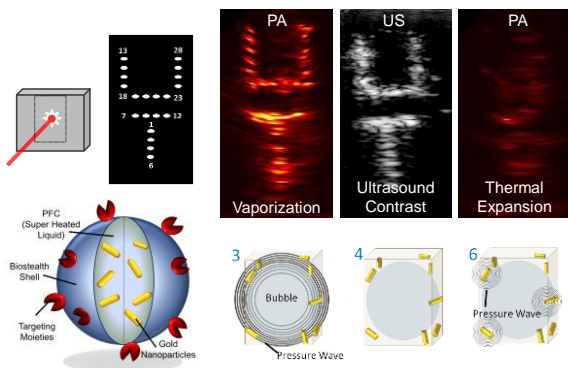
Perfluorocarbon NanoDroplets for PA and US Imaging

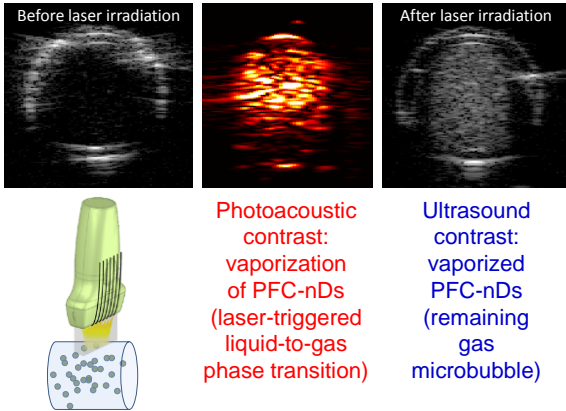


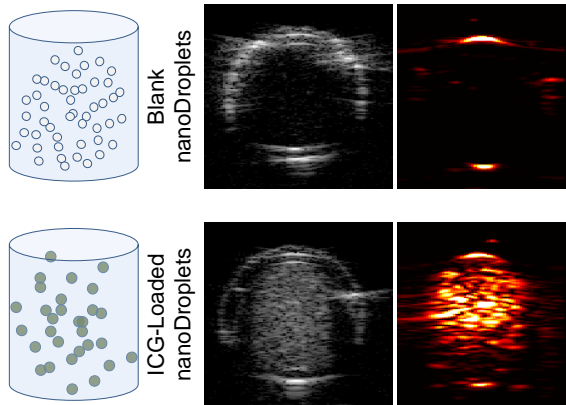
2.5-in-1 Contrast Mechanisms



2.5-in-1 Contrast Mechanisms

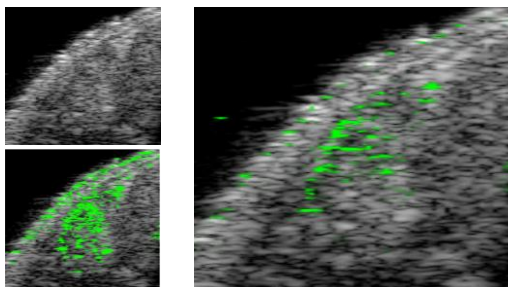




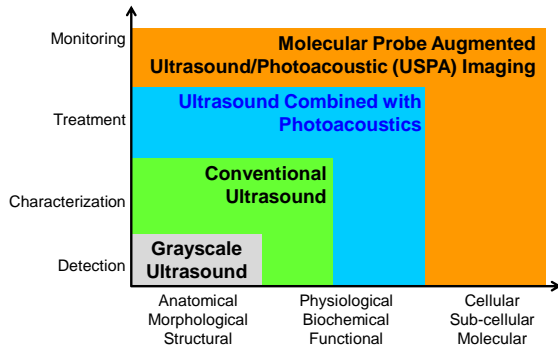


USPA Detection of SLN and Micrometastases

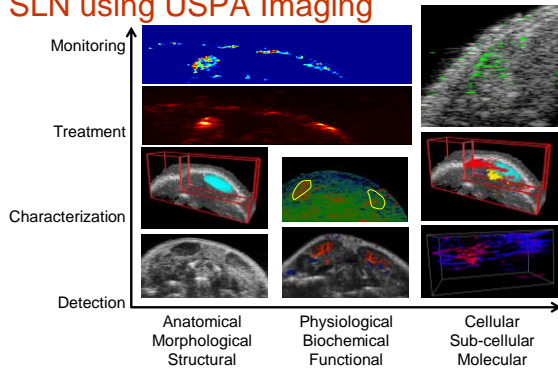
- Injection of molecularly targeted dual contrast agent – PFC nanodroplets



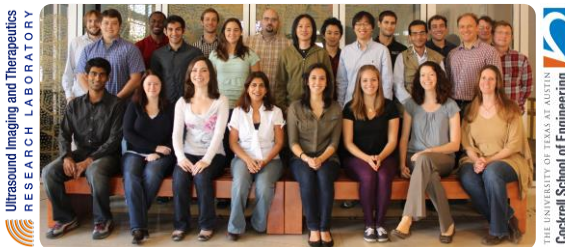
Combined Ultrasound and Photoacoustics



Detection/Characterization/Therapy of SLN using USPA Imaging



Acknowledgements



Collaborators from:
University of Texas at Austin
BME, ECE, ChE, ME, Chemistry
Pharmacy, Dell Medical School
UT MD Anderson Cancer Center
UT Health Science Center Houston
University of Alabama at Birmingham

Industrial partners:
Visualsonics, Inc.
NanoHybrids, Inc.
Athera Medical, Inc.
Sonosite, Inc.
Verasonics, Inc.
TVL, TMA, ATI

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National Science Foundation
Breast Cancer Research
Foundation
Department of Defense
American Heart Association

Clinical Translation of Ultrasound-Guided Photoacoustic Imaging

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